

Gradients in myocardial blood flow, metabolism and mechanics across the ischemic left ventricular wall

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9. SUMMARY AND CONCLUSIONS

The aim of the present study was to investigate the relation between fiber shortening, blood flow and metabolism in the various layers of the left ventricular wall during two hours of ischemia. Special attention is paid to the cessation of fiber shortening and the accumulation of non-esterified fatty acids (NEFA) in ischemic myocardium. Also the effect of artificially elevated of arterial NEFA concentrations on the ischemic myocardium has been studied. The experiments were performed on anesthetized open-chest dogs. Myocardial blood flow (MBF) and metabolism were determined in the inner (subendocardial), middle and outer (subepicardial) layers of the left ventricular wall, whereas fiber shortening was assessed in the inner and outer layers. Fiber shortening was estimated from the epicardial surface deformation (Arts and Reneman, 1980). MBF was determined with the radioactive microsphere method (reviewed by Heymann et al, 1977). Myocardial metabolism was assessed by determination of the contents of ATP, creatine phosphate, glycogen, NEFA, triacylglycerol and phosphoglycerides in tissue samples from the myocardial wall, and of myocardial uptake from the blood of oxygen, glucose, lactate, NEFA, triacylglycerol, inorganic phosphate and potassium. Systemic hemodynamic variables were measured as usual. Cardiac output was measured by thermodilution according to Snoeckx et al (1976).

Ischemia was induced by partial or complete occlusion of the left anterior interventricular coronary artery (LAICA) by inflating a cuff around this artery. The degree of partial occlusion (=stenosis) was estimated from the mean coronary artery pressure (p_{cor}) distal to the stenosis. An appropriate degree of stenosis was obtained by careful manual inflation of the cuff until a mean p_{cor} of 3.3 kPa (25 mmHg) was reached. Mean p_{cor} was kept constant during the experimental period with a servosystem controlled by this pressure.

Before studying the effects of ischemia, the experimental model was evaluated during 2 hours without intervention (chapter 4). During this period, MBF as well as the hemodynamical, regional mechanical and metabolic variables were stable (i.e. did not change significantly). However, serial tissue sampling during the experiments caused significant decreases in epicardial deformation and MBF. Therefore, it was decided to terminate each experiment after two biopsies had been taken, one from the ischemic (LAICA) and one from the non-ischemic (LCCA) area. Changes due to ischemia can be evaluated by comparing the content of a substance in the LAICA biopsy with that in the

LCCA biopsy of the same experiment since during normal perfusion, the contents of the various substances were similar in both regions.

In chapter 4, it has also been shown that MBF in the outer layer of the left ventricular free wall is inhomogeneously distributed. MBF in these layers was higher near the apex than near the base and lower in the posterior than in the anterior region of the free wall. The cause of these differences is incompletely understood.

In chapter 5, the prediction of fiber shortening in the inner layers from epicardial deformation was validated. Epicardial minimal (e_{\min}) and maximal shortening (e_{\max}) were calculated from the measured epicardial shortening in circumferential and base-to-apex direction and the shear angle during the ejection phase (section 3.3). According to a mathematical model of the left ventricle (Arts, 1978, 1980, 1982a,b), the direction of e_{\max} was approximately equal to the fiber direction in the outer layers and the direction of e_{\min} was close (within 0.3 rad) to the fiber direction in the inner layers. The relation between e_{\min} and shortening in the inner layers in the direction of e_{\min} (called e_{endo}) was subject of a study where deformation was assessed simultaneously at the epicardium and in the inner layers by measurement of mutual movement and angulation of three needles pierced into the myocardial wall. During normoxia and ischemia, e_{\min} was found to be clearly related to fiber shortening in the inner layers, so that information about this shortening could be obtained from measurements at the epicardium.

After onset of ischemia e_{\min} started to decrease 2 s (occlusion, chapter 5) and 30 s (stenosis, chapter 6) before a significant change in e_{\max} could be detected. e_{\min} transiently reached negative values (i.e. lengthening of the fibers), which was more pronounced after occlusion than after stenosis. However, e_{\max} gradually decreased to about 20% of the pre-ischemic values within the first min and the median did not reach negative values. These results show that after onset of acute ischemia fiber shortening is earlier and more severely affected in the inner than in the outer layers. Transmural differences in shortening are pronounced during the first half min but relatively small after one min of ischemia.

In chapter 6, the relation between this early cessation of shortening after stenosis of a coronary artery and the changes in MBF and metabolism was studied. Stenosis caused a decrease in MBF of 68% and 81% in the inner layers and of 36% and 54% in the outer layers after 1 and 5 min of ischemia, respectively. Within 5 min of ischemia, no significant changes could be detected.

ted in myocardial ATP content but creatine phosphate content in the inner layers had halved within one min of ischemia and further decreased gradually in all layers during the next 4 min. Significant release of inorganic phosphate into the venous blood draining the ischemic area, within half a minute of ischemia also indicated the early breakdown of energy-rich phosphates. Glycogen contents in the various layers were hardly affected within 5 min of ischemia. These results were compared with the current hypotheses on the cause of the early cessation of contractile activity as discussed in section 2.1.2. Based on the results of the present study the early cessation of shortening might be explained by the decrease in free energy provided by ATP hydrolysis. A major inhibition of shortening by local depletion of glycogen or accumulation of inorganic phosphate per se seems unlikely.

Because of the higher oxygen delivery (higher blood flow and probably small differences in O_2 extraction) to the outer than to the inner layers and because of the relatively small differences in the changes in fiber shortening during ischemia, it is suggested that the outer layers are impeded to shorten by the inner layers and are forced to bear stress which cannot be built up by the inner layers.

During the first 5 min of ischemia, the lactate release from the affected myocardium could only partially be explained by the uptake of glucose. An early, but hardly measurable glycogenolysis might be involved.

In chapter 7, the time course of blood flow, fiber shortening and metabolism during two hours of ischemia was studied. At the constant low perfusion pressure (see above), MBF to the whole ischemic area did not change significantly between 10 and 120 min of ischemia. In contrast, the relative underperfusion of the inner layers became worse at longer duration of ischemia. The tissue contents of ATP, creatine phosphate and glycogen after 10, 60, and 120 min of ischemia were diminished, the lowest values being reached in the inner layers. ATP content in the inner layers gradually declined to 28% of the normoxic value after 120 min of ischemia. In the inner layers, the creatine phosphate content after 60 min was about 25% of the normoxic value, but increased to about 50% of the normoxic value after 120 min. Glycogen content in the inner layers gradually decreased to 38% of the normoxic content after 120 of ischemia. The already severely affected regional myocardial fiber shortening after 10 min of ischemia, subsequently deteriorated during the next 110 min; e_{\max} declining to a slightly more pronounced degree than e_{\min} . These results show that transmural differences in metabolism invariably exist

between 10 and 120 min, the transmural gradient in blood flow even increases within this period, and the differences in shortening in the myocardial wall tend to decrease.

No significant increase in NEFA content was observed 10 min after onset of ischemia. In the outer layers NEFA content showed a biphasic pattern with a maximum increase (about 3-fold) after 60 min of ischemia, whereas in the inner layers NEFA content gradually increased to approximately 4 times the normoxic values after 120 min. In the outer layers an important part of this accumulation may be caused by lipolysis of endogenous triacylglycerol or fatty acids extracted from the blood. The relatively highest increase in linoleic and arachidonic acid in the inner layers suggests that lipolysis of phosphoglycerides is an important source of these NEFA. NEFA accumulation in the inner layers after 60 min and in all layers after 120 min, proved to be related to MBF and ATP content of the ischemic area. After 120 min of ischemia NEFA contents were found to be increased when MBF was lower than $0.3 \text{ ml} \cdot \text{min}^{-1} \cdot \text{g}^{-1}$ and ATP content was lower than $10 \mu\text{mol} \cdot \text{g}^{-1}$ dry weight.

From these data it has been hypothesized that the NEFA accumulation in ischemic myocardium is likely not the cause of impaired mechanical performance and metabolism as well as cell death.

In chapter 8 the effect of elevated arterial NEFA concentrations on MBF, myocardial metabolism and hemodynamics during ischemia was studied. NEFA concentrations were elevated by intravenous injection of heparin, intralipid or both substances (intralipid-heparin).

After elevation of NEFA concentrations by heparin or intralipid-heparin, heart rate gradually increased, while aortic pressure tended to decrease.

Slight elevation of arterial NEFA levels (up to 0.53 mM), had no significant effect on total MBF and uptake of glucose, NEFA, and oxygen or release of lactate in the ischemic myocardium. However, elevating arterial NEFA levels up to 0.81 mM (by intralipid-heparin), significantly decreased total MBF (16%), ratio of blood flow in the inner and outer layers (13%) and oxygen uptake (34%) in the ischemic myocardium, and resulted in release of lactate from this area. The release of potassium, inorganic phosphate and H^+ as well as plasma CO_2 concentration were not influenced. Neither was the uptake of glucose and NEFA.

Although the role of the simultaneously elevated arterial triacylglycerol levels can not be excluded, these findings suggest that elevated arterial NEFA concentrations can decrease MBF and augment lactate production. Glycoly-

sis in the ischemic myocardium is not inhibited.

In short the findings of the present study indicate that:

- fiber shortening in the various layers of the left ventricular wall can be estimated from myocardial deformation during the ejection phase as measured at the epicardial surface
- after onset of ischemia, cessation of fiber shortening starts in the inner layers and subsequently is seen in the outer layers
- the cessation of fiber shortening after inducement of ischemia can not be ascribed to depletion of ATP or creatine phosphate stores
- during ischemia of one min and longer, transmural differences in fiber shortening are small compared to differences in blood flow and metabolic variables, suggesting that fiber shortening in the outer layers seems to be impeded by the severely affected function of the inner layers
- accumulation of NEFA in ischemic myocardium could be detected at 60 and 120 min, but not after 10 min of ischemia
- the changes in mechanical function and metabolism in the ischemic myocardium are not necessarily due to NEFA accumulation
- an important part of the accumulated NEFA, especially in the inner layers after 120 min of ischemia, is probably derived from endogenous phosphoglycerides
- after 120 min of ischemia, accumulation of NEFA is highest in the inner layers and lowest in the outer layers. The extent of accumulation does not depend on the myocardial layer itself but on the amount of MBF and the content of ATP in the ischemic myocardium: increased NEFA contents are observed when myocardial blood flow is lower than $0.3 \text{ ml} \cdot \text{min}^{-1} \cdot \text{g}^{-1}$ and when the ATP content is lower than $10 \mu\text{mol} \cdot \text{g}^{-1}$ dry weight.
- artificial 4-fold elevation of arterial NEFA concentrations by administration of intralipid-heparin causes a 16% decrease in ischemic myocardial blood flow.

10. SAMENVATTING

Het hart is een holle spier, die dienst doet als pomp om het bloed door de bloedvaten voort te stuwen. De rechter en de linker harthelft bestaan ieder uit een dunwandige boezem, waarin de aders uitmonden, die het bloed naar het hart terugvoeren en een sterk gespierde kamer die het bloed de slagaders inpompt. De rechter harthelft ontvangt het zuurstofarme bloed uit de aders van het lichaam en pompt het naar de longen (de kleine bloedsomloop). De linker harthelft ontvangt het zuurstofrijke bloed uit de longen en pompt het naar alle organen van het lichaam (de grote bloedsomloop).

Het hart verkrijgt energie voor het rondpompen van het bloed door glucose, melkzuur en vetten te verbranden met behulp van zuurstof. Deze zuurstof wordt aangevoerd door het bloed in de kransslagaders. Vernauwing of afsluiting van een kransslagader leidt tot zuurstofgebrek (=ischemie) van de hartspier. Het optreden van ischemie van de hartspier leidt binnen een minuut tot verminderde samentrekking van de spiervezels (dus verminderde pompfunctie) en binnen een tot twee uur tot celdood. Indien dit laatste optreedt bij patienten, spreekt men van een hartinfarct.

Tijdens de hartcyclus is de doorstroming van de kransslagaders aan sterke veranderingen onderhevig, vooral in de linker kamer. Om het bloed de slagaders van het lichaam in te pompen wordt door samentrekking van de kamers een hoge druk opgebouwd in de kamerholte, die zich ook voortplant in de wand van de kamers. Deze weefseldruk belemmert echter de doorbloeding van de spierwand. Deze belemmering is het sterkst in de binnenste lagen van de linker kamerwand, waar de weefseldruk het hoogst is. Onder normale omstandigheden wordt het tekort aan doorbloeding tijdens samentrekking gecompenseerd door een versterkte doorstroming wanneer de hartspier ontspannen is. Echter wanneer de normale doorstroming door de kransslagaders gehinderd wordt door een vernauwing van het vat, schiet deze compensatie te kort. Hierdoor treedt ischemie het snelst op in de binnenste lagen van de linker kamer. Bij patienten wordt een hartinfarct overwegend in de binnenste lagen gevonden en experimenteel is aangetoond dat bij belemmerde doorstroming van de kransslagaders niet alleen de doorbloeding maar ook de stofwisseling van de binnenste lagen het sterkst verstoord wordt door ischemie.

Weinig is nog bekend over de verschillen in spiervezelverkorting binnen de kamerwand omdat het technisch moeilijk is de spiervezelverkorting te meten in de binnenste lagen van de wand.

Verhoogde concentraties van onveresterde (=vrije) vetzuren, zowel in de cel als in het bloed, worden door verschillende onderzoekers als schadelijk beschouwd voor het ischemische hartspierweefsel.

In het onderzoek, beschreven in dit proefschrift, is de relatie bestudeerd tussen doorbloeding, spiervezelverkorting en stofwisseling in verschillende lagen van de ischemische linker kamerwand. Het onderzoek vond plaats in honden met open borstkas, onder volledige verdoving. Ischemie van een gedeelte (10-20%) van de linker kamerwand is veroorzaakt door vernauwing of afsluiting van de voorste afdalende tak van de linker kransslagader.

De belangrijkste conclusies uit dit onderzoek zijn:

- spiervezelverkorting in de verschillende lagen van de linker kamerwand kan bepaald worden uit de vormverandering van deze wand, zoals deze gemeten wordt aan het buitenoppervlak van de ventrikel (het epicard).
- na het begin van ischemie neemt de spiervezelverkorting in de binnenste lagen van de kamerwand het eerst en het sterkst af, gevolgd door een meer geleidelijke afname in spiervezelverkorting in de buitenste lagen.
- de afname van de spiervezelverkorting na het aanleggen van ischemie, kan niet toegeschreven worden aan depletie van ATP of creatine fosfaat voorraden.
- gedurende ischemie van een minuut en langer zijn de verschillen tussen de binnenste en buitenste lagen van de kamerwand wat betreft spiervezelverkorting relatief klein ten opzichte van de verschillen in doorbloeding en stofwisseling. Een mogelijke verklaring hiervoor is dat spiervezelverkorting in de buitenste lagen van de kamerwand belemmerd wordt door de ernstig aangedane functie van de binnenste lagen van deze wand.
- ophoping van onveresterde vetzuren in ischemisch hartspierweefsel kon niet aangetoond worden na 10, maar wel na 60 en 120 min ischemie.
- een belangrijke oorzaak van de ophoping van onveresterde vetzuren, vooral in de binnenste lagen na 120 min ischemie, is waarschijnlijk de afbraak van fosfoglyceriden (fosfolipiden), stoffen die voorkomen in membranen van de cel.
- na 120 min ischemie is de ophoping van onveresterde vetzuren het grootst in de binnenste lagen en het kleinst in de buitenste lagen van de linker kamerwand. De grootte van deze vetzuurophoping is echter niet afhankelijk van de laag in de wand, maar van de mate van afname van de doorbloeding en het ATP-gehalte in het ischemische hartspierweefsel: een verhoogd gehalte

- onveresterde vetzuren is aangetroffen als de doorbloeding lager is dan $0.3 \text{ ml.min}^{-1}.\text{g}^{-1}$ en als het ATP gehalte lager is dan $10 \mu\text{mol.g}^{-1}$ drooggewicht.
- de veranderingen in mechanische functie en stofwisseling in de ischemische linker kamerwand zijn waarschijnlijk niet te wijten aan de ophoping van onveresterde vetzuren, zoals wel is voorgesteld door andere onderzoekers op grond van proeven met geïsoleerde harten of enzymsystemen.
 - een viervoudige kunstmatige verhoging van de concentratie onveresterde vetzuren in het bloed veroorzaakte een afname van 16% van de doorbloeding in het ischemische deel van de linker kamerwand.